IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA UK LIMITED, IPR PHARMACEUTICALS, INC., and PLAINTIFFS SEIYAKU KABUSHIKI KAISHA,	)	
Plaintiffs,	)	
v.	)	C.A. No. 10-915-LPS
WATSON LABORATORIES, INC. (NV)	)	
Defendant.	)	

WATSON'S POST-TRIAL ANSWERING BRIEF

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TABLE OF CONTENTS

Page No.

TABLE OF CONTENTS
(continued)

Page No.

TABLE OF CONTENTS
(continued)

Page No.

TABLE OF AUTHORITIES

Page No(s).

TABLE OF AUTHORITIES
(continued)

Page No(s).

TABLE OF AUTHORITIES
(continued)

Page No(s).

STATUTES

OTHER AUTHORITIES

I. INTRODUCTION

Watson's rosuvastatin zinc product does not infringe the '314 patent literally or under the doctrine of equivalents. Watson's product is outside the literal scope of the claims as determined by this Court, and the doctrine of equivalents is not available to Plaintiffs at least because Plaintiffs elected to narrowly define and claim their invention, excluding foreseeable alternative salts such as the zinc salt, and because Watson's product is substantially different from the narrow subset of claimed rosuvastatin salts.

Rather than use the broad, ordinary meaning of "pharmaceutically acceptable salt," Plaintiffs intentionally chose a narrower definition that included salts that are formed only by ions of alkali metals, alkaline earth metals and unsubstituted ammonium. This extremely narrowed group excluded zinc and dozens of other salt-forming ions that were known and claimed in the prior art of statin salts. Having made these elections in drafting their patent application, Plaintiffs cannot now recapture these salt-forming ions through the doctrine of equivalents without seriously undermining the critical public notice function of the patent.

The doctrine of equivalents is not available as insurance against the foreseeable consequences of Plaintiffs' decision to narrowly claim their invention. Rather, the Supreme Court has stated that it is an equitable principle premised on language's inability to capture the essence of innovation and applies where it would be inequitable to hold an applicant to his own words because some subtlety of language or technological complexity obfuscated his ability to appreciate the significance of his chosen language. Similarly, application of the doctrine is appropriate where the alleged equivalent is a product of subsequent technological change in the art, which the applicant could not have foreseen and drafted its claims to encompass.

Here, neither equitable justification is present to allow application of the doctrine of equivalents. The language certainly existed to literally cover zinc and other "pharmaceutically acceptable salts." Indeed, but for Plaintiffs' narrow definition, these other salts would have been covered within the normal meaning of "pharmaceutically acceptable salts." Moreover, the evidence clearly establishes that zinc was among other salt-forming ions known and claimed in the prior art of statin salts. The Federal Circuit has acknowledged that the law imposes the burden of careful drafting upon the patentee. Accordingly, in a line of authority from *Sage* to *Wrigley*, the Federal Circuit consistently has barred the doctrine of equivalents where the applicant deliberately claimed his invention narrowly, and the potential interchangeability of the alleged equivalent was at least foreseeable at the time of drafting.

Watson presented voluminous documentary evidence and the expert testimony of Dr. Clayton Heathcock regarding the known potential suitability of zinc to make a pharmaceutically acceptable statin salt. Dr. Heathcock, the only testifying expert in this case who had experience in the statin field at the relevant time, cited numerous prior art patents obtained by leaders and true pioneers in the statin field, such as Sankyo (which discovered the first statin) and Merck (which brought the first statin to market). Some prior art patents were cited by Plaintiffs either within the text of the '314 patent itself or during its reissue proceedings, and some even expressly claimed zinc salts of statins. Even Plaintiffs' expert agreed that a person of ordinary skill not only would have known that zinc could be used to form pharmaceutically acceptable salts, but actually could have made a zinc statin salt. Thus, the prior art clearly establishes the foreseeability of zinc as a statin salt-forming ion.

Allowing Plaintiffs to now cover other foreseeable pharmaceutically acceptable statin salt-forming ions would run counter to the authority in *Sage* and *Wrigley* and would

impermissibly eliminate Plaintiffs' entire special definition from the patent, thereby eviscerating the public notice function of the patent.

Therefore, as a matter of law, Watson is entitled to judgment of no infringement under the doctrine of equivalents.

In the alternative, the Court should enter judgment for Watson because Plaintiffs have not met their burden of proving that Watson's rosuvastatin zinc product is insubstantially different from the claimed rosuvastatin salts. Indeed, the evidence reflects substantial differences between them.

II. PLAINTIFFS ARE PRECLUDED FROM ASSERTING THE DOCTRINE OF EQUIVALENTS

A. Plaintiffs' Decision To Exclude Foreseeable Alternatives Through Narrow Claiming Precludes Application Of The Doctrine Of Equivalents

1. The Federal Circuit Bars Equivalence For Narrow Claims That Exclude Foreseeable Alternatives

The Supreme Court has long recognized that "the doctrine of equivalents, when applied broadly, conflicts with the definitional and public-notice functions of the statutory claiming requirement." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997). "In recognition of this risk, and in an effort to strike the proper balance between protecting patentees while also providing sufficient notice to the public, various rules of law have emerged to constrain when and how the doctrine of equivalents is to be applied." *Freedman Seating Co. v. American Seating Co.*, 420 F.3d 1350, 1358 (Fed. Cir. 2005). These rules or principles together guide a court in determining whether a patentee is entitled to expand its claimed invention, via the doctrine of equivalents, beyond the literal terms by which it chose to define its invention.

Thus, the fundamental touchstone of the various limitations on the doctrine of equivalents is the critical public notice function of the patent. Under this subsuming principle, the public has

the right to rely on the boundaries made manifest by a patentee's choices in drafting the specification and claims. Indeed, it is well-settled that "many limitations warrant little, if any, range of equivalents." *Moore U.S.A., Inc. v. Standard Register Co.*, 229 F.3d 1091, 1106 (Fed. Cir. 2000). "Thus, for a patentee who has claimed an invention narrowly, there may not be infringement under the doctrine of equivalents in many cases, even though the patentee might have been able to claim more broadly." *Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1424 (Fed. Cir. 1997).

This principle flows from the Supreme Court's recognition that "[t]he doctrine of equivalents is premised on language's inability to capture the essence of innovation . . . ." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 734 (2002). Accordingly, the ban applies where (a) the patentee's ability to capture his invention was not impeded by inherent capabilities of language or technical complexity, and (b) the accused equivalent was known or at least foreseeable at the time of the alleged invention. *Sage*, 126 F.3d at 1424-25; *Freedman*, 420 F.3d at 1362; *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1366 (Fed. Cir. 2012).

For example, the Federal Circuit in *Sage* affirmed summary judgment of no infringement under the doctrine of equivalents based on the inherent narrowness of the chosen claim language. The patent in that case related to containers for the disposal of medical instruments, and included a claim for a container with a "slot at the top of the container body," "a first constriction extending *over said slot*," and a "second constriction extending *beneath said slot*." *Sage,* 126 F.3d at 1422 (emphasis added). Although the accused product did not have a constriction extending over its slot at the top, the patentee "essentially argue[d] that having two constrictions below the top of the container is the same, for purposes of infringement, as having one

constriction above and one constriction below." *Id.* at 1424. The district court granted summary judgment that the patentee was barred from pursuing its doctrine of equivalents theory. *Id.*

The Federal Circuit based its decision on the patentee's narrow claim language using the terms "over" and "beneath," the absence of any linguistic or technological impediment to claim its invention more broadly, and the foreseeability of the accused equivalent structure:

> A skilled patent drafter would foresee the limiting potential of the "over said slot" limitation. No subtlety of language or complexity of the technology, nor any subsequent change in the state of the art, such as later-developed technology, obfuscated the significance of this limitation at the time of its incorporation into the claim. . . . If Sage desired broad patent protection for any container that performed a function similar to its claimed container, it could have sought claims with fewer structural encumbrances.

Id. at 1425.

Similarly, the Federal Circuit in *Freedman* barred application of the doctrine of equivalents based on the same analysis and protection of the public's right to rely on a patentee's decision to narrowly claim its invention. The patent at issue in *Freedman* was to a stowable seat having a support structure known in the art as a "four bar mechanism." *Freedman*, 420 F.3d at 1353-54. The claim itself, however, was not to a generic "four bar mechanism," but instead to a particular arrangement with the moveable end of one bar "slidably mounted" to the seat base as part of a slider crank. *Id.* Although the accused device also could be described as a "four bar mechanism," the accused equivalent structure was "rotatably mounted" rather than "slidably mounted" to the seat base. *Id.* The district court granted plaintiff's motion for summary judgment of infringement under the doctrine of equivalents. *Id.* at 1351.

The Federal Circuit reversed, holding that plaintiff was precluded as a matter of law from asserting its doctrine of equivalents theory. The court emphasized the patentee's chosen narrow claim language, the lack of linguistic or technological impediments to broader claim language,

and the foreseeability of other "four bar mechanism" support structures at the time. As a result, explained the Court, the public was justified in relying on the patentee's specific language in assessing the bounds of the invention:

> Members of the public were therefore justified in relying on this specific language in assessing the bounds of the claim. Accordingly, we think that to now say the claims include other four bar mechanisms under the doctrine of equivalents would unjustly undermine the reasonable expectations of the public.

Id. at 1362 (citations omitted).

The Federal Circuit's decision in *Wrigley* reaffirmed the principle that the doctrine of equivalents is not available to enlarge narrowly-drawn claims to cover alleged equivalents that were foreseeable and easily-described by the patentee at the time. It also confirmed that foreseeability does not require the prior art to disclose anything beyond the mere potential suitability of the alleged equivalent, and can even suggest that the equivalent could be less than ideal in certain circumstances. *See Wrigley*, 683 F.3d at 1366; *see also Duramed Pharms., Inc. v. Paddock Labs., Inc.*, 644 F.3d 1376, 1381-82 (Fed. Cir. 2011).

The inventor in *Wrigley* defined his invention by selecting a subset of the group of compounds known as "N-substituted-p-menthane carboxamides." Specifically, he chose to restrict his invention to only those "N-substituted-p-menthane carboxamides" described by a particular formula, with specified permissible substituents at various positions. *Wrigley*, 683 F.3d at 1359, 1365. The competitor's alleged equivalent, called "WS-23," was a carboxamide outside the claimed subset. *Id*. The district court granted summary judgment of no infringement, primarily on the ground that the patentee's narrow claim implicitly excluded or disavowed the alleged equivalent. *Id.* at 1359. The Federal Circuit affirmed. *Id*. at 1365-66.

In finding the limitation to have been narrowly claimed, the court explained that although the specification discussed "N-substituted-p-menthane carboxamides" generally, the patentee

had chosen to claim only the subset of such compounds defined by its formula and substituents. *Id.* at 1366 (citing *Tanabe Seiyaku Co. v. U.S. Int'l Trade Comm'n*, 109 F.3d 726, 732 (Fed. Cir. 1997) and *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 955 (Fed. Cir. 2006)). The court found that the prior art taught the claimed equivalent use of WS-23 in combination with menthol, and found that even though WS-23 had not been approved for commercial marketing at the time, it was sufficient that "the inventors were on notice of the potential interchangeability of WS-23 and [the claimed compound]." *Id.* at 1359, 1366.

Finally, the limiting principles on the doctrine of equivalents can overlap in practical application to produce the same results, particularly when dealing with narrow claims. This is especially so where, as here, a patentee acting as his own lexicographer provides a definition that limits the plain meaning of a term. The Federal Circuit in *AstraZeneca AB v. Mutual Pharm. Co.*, 384 F.3d 1333, 1340 (Fed. Cir. 2004), found that such a definition by itself implicitly excluded the unclaimed alternatives then known in the art. The patent in *AstraZeneca* covered extended-release felodipine tablets sold by AstraZeneca under the trade name Plendil®. *AstraZeneca*, 384 F.3d at 1335. Claims to the composition and process for making the composition required a "solubilizer." The court found that instead of relying on the plain meaning of "solubilizer," which comprised three possible sub-classes, the patentee chose to act as its own lexicographer by defining solubilizer to include only one of the known sub-classes, namely "surfactants." *Id.* at 1336, 1339-40. Because the two other known sub-classes fell within the ordinary meaning of "solubilizer," the court concluded that the patentee's decision to limit the ordinary meaning of "solubilizer" to "surfactants" implicitly disavowed coverage of the two other sub-classes. *Id*. Specifically, the court concluded that "[t]he inventors' lexicography *alone* works an implicit disavowal of nonsurfactant solubilizers . . . .", before proceeding with its

analysis of the rest of the specification, ultimately finding no infringement under the doctrine of equivalents. *Id.* at 1340, 1342 (emphasis added); *see also Tanabe*, 109 F.3d at 731-32 (finding exclusion of ketones other than acetone, where acetone was the only ketone specified in narrowly drafted claim).

2. Plaintiffs Chose To Narrowly Define Their Claim To Cover Only A Subset Of Salts Included Within The Ordinary Meaning Of "Pharmaceutically Acceptable Salt"

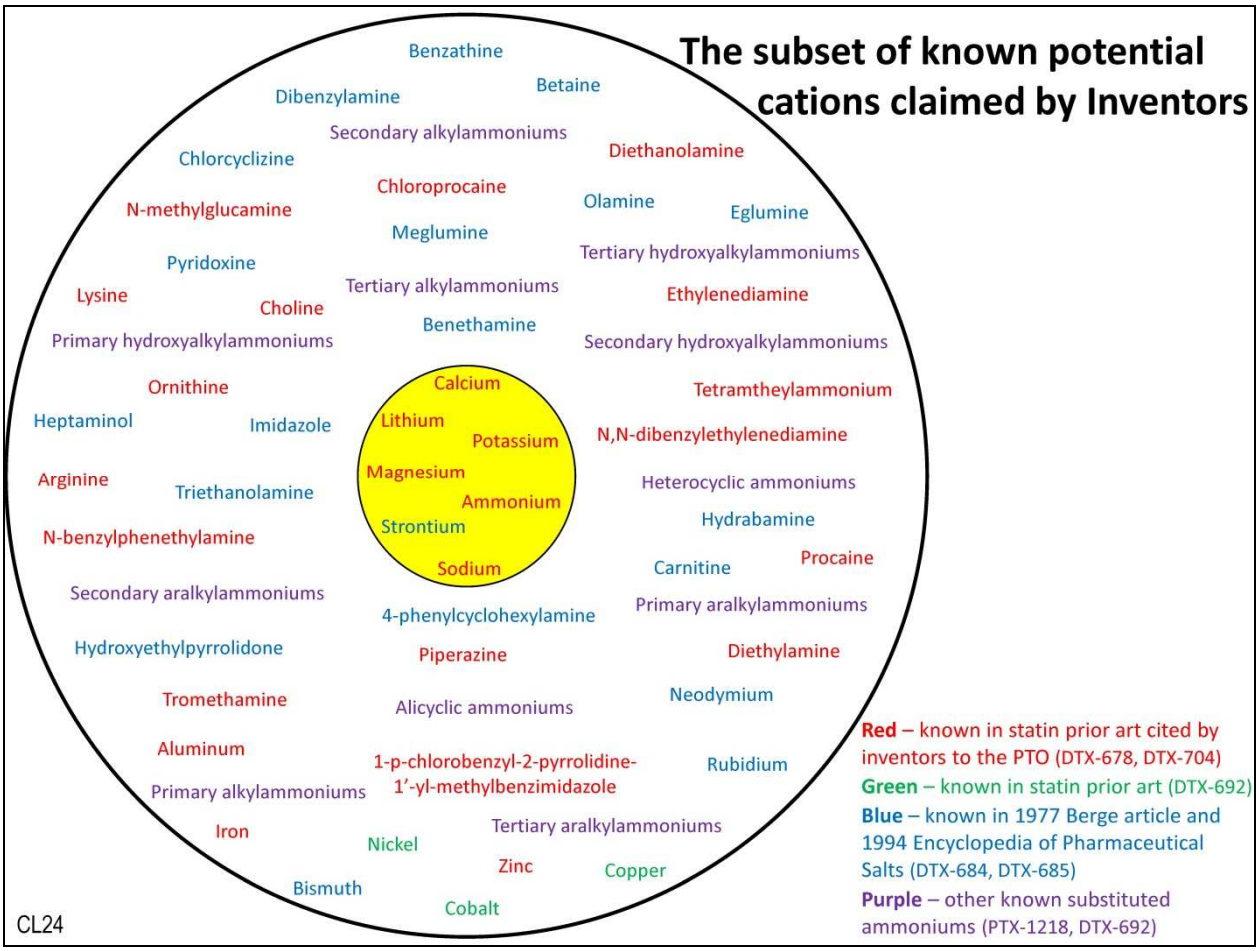
While Claim 6 broadly requires any "pharmaceutically acceptable salt," Plaintiffs insisted on providing their own definition of that term in the specification. Watson's expert Dr. Heathcock testified that the ordinary meaning of "pharmaceutically acceptable salt," which would have controlled in the absence of Plaintiffs' definition, would have been considered extremely broad by the person of ordinary skill in the art because it would have included every salt that delivered the active moiety and was not poisonous. DFF ¶¶ 16-21. In contrast to that broad definition, Plaintiffs' definition is unambiguous and is confined to salts formed by ions of alkali metals, alkaline earth metals and unsubstituted ammonium. *Id*.

Dr. Heathcock provided further evidence of the claims' narrowness in view of how statin salt ions had been claimed in the prior art. DFF ¶¶ 22-29. The patents that Dr. Heathcock presented were not merely one or two obscure patents from unknown inventors. Rather, they were a collection of patents from the companies that were pioneers and leaders in the statin field. *Id*.

For example, Dr. Heathcock identified a vast array of statin and carboxylic acid patents from the relevant time that utilized exemplary and open-ended salt definitions, showing that it was a very common practice for those of skill in the art to claim and define statin salts in a non-

limiting manner in contrast to the '314 patent, as even Plaintiffs' expert Dr. Roush was obliged to admit. DFF ¶ 21; Tr. 621:20-24.

As discussed in detail below and in Watson's proposed Findings of Fact, the following representative summary of claimed versus unclaimed ions demonstrates Plaintiffs' decision to claim only a fraction of the ions already known in the art. DFF ¶¶ 30-31.



In the Figure above, the small yellow circle contains the salt-forming ions that were covered by Plaintiffs' special definition and disclosed in the art. As indicated in the legend, the red ions were disclosed in statin prior art patents actually cited by Plaintiffs to the PTO. The green ions were disclosed in additional statin prior art patents. The blue ions are from general pharmaceutical treatises. It is important to note that this representation understates the number

of specific unclaimed ions. This is because the purple entries are not specific ions, but instead are genera of dozens, if not hundreds, of salt-forming ions found within the statin-specific prior art.

Information in the Figure above was supported by Dr. Heathcock's detailed trial testimony. DFF ¶¶ 22-29. Dr. Heathcock first pointed to the '314 patent itself, which discloses the '784 prior art patent covering the commercial drug simvastatin, or Zocor®. Tr. 720:18-722:6; DTX-676 at 1:20. Within the cited Zocor® Patent, there is a description of salts showing that the inventors contemplated the use of many salts outside the scope of the defined salts in the '314 patent. Specifically, the Zocor® Patent claims "pharmaceutically acceptable salts" of the statins, and expressly defined that term to include zinc and aluminum salts, as well as a dozen substituted ammonium salts, all of which fell outside the scope of the defined salts in the '314 patent. Tr. 720:18-722:6; DTX-704 (15:3-13, 26:60). Additionally, the Zocor® Patent defines "pharmaceutically acceptable salt" using the open-ended phrase "include," encompassing within its claims even more salts than those it expressly identified. *Id.*

The Zocor® Patent would have been significant to a person of ordinary skill in the statin field not only because it was specifically cited in the '314 patent itself, but because Zocor® had already achieved $300 million in first-year sales in Canada, and would have been considered to be a future blockbuster even before its approval in the U.S. DFF ¶ 22. Thus, the Zocor® Patent was already an historic and commercially significant reference to persons of ordinary skill in the statin art, and likely the reason why Plaintiffs cited it in the '314 patent. *Id.*

Moreover, as the first company to successfully market a statin, Merck was considered the leading statin research company at the time. Tr. 727:5-15. Merck's prolific research at the time resulted in at least seven additional statin patents identified by Dr. Heathcock that broadly

describe pharmaceutically acceptable statin salts as including not only some of the salts identified by Plaintiffs, but additional salts outside Plaintiffs' definition, including zinc and about a dozen substituted ammonium salts. Tr. 725:6-732:16; DTX-686 (4:55-64), DTX-687 (4:63-5:3), DTX-691 (4:37-45), DTX-695 (5:38-46), DTX-696 (5:31-39), DTX-697 (2:34-43), DTX-698 (3:35-44). One Merck patent also disclosed six working examples of substituted ammonium salts falling outside of Plaintiffs' definition, emphasizing their research interest in such salts. Tr. 729:13-730:4; DTX-686 (16:40-68).

Plaintiffs attempt to discount the significance of Merck's prolific statin work because the patents contain a similar salt definition. PPFF ¶ 47. However, Dr. Heathcock provided unrebutted testimony that the use of similar disclosures among researchers in the same facility is not surprising. DFF ¶ 24. Moreover, Dr. Heathcock provided unrebutted testimony that the various Merck patents could be viewed as a collective Merck disclosure presented in numerous patents, which would make it more likely that a person of ordinary skill would be aware of such work. *Id.* Thus, Dr. Heathcock concluded that the similarity in Merck's salt disclosure would not change his opinion, and there would be no reason for a person of ordinary skill in the art to ignore or disregard an expressly-identified salt because it shows up multiple times in a similar salt disclosure. *Id.*

Dr. Heathcock also relied on a second patent disclosed by the inventors in the intrinsic record of the '314 patent, the '185 patent by Chucholowski. DFF ¶ 25; DTX-699 (8:40-43). The Chucholowski patent was a prior art reference of particular pertinence because it concerned pyrimidine statins, which are the same type of statins as rosuvastatin. DFF ¶ 25. Indeed, Plaintiffs' expert Dr. Roush characterized pyrimidine prior art as "pertinent and related as close prior art," and Plaintiffs placed this patent first in its list of prior art submitted to the PTO during

the '314 reissue. Tr. 549:22-550:6, 725:20-726:18; DTX-678 at 63. Importantly, the Chucholowski patent discloses that pharmaceutically acceptable salts that can be formed with pyrimidine statins include not only those Plaintiffs defined, but also aluminum, iron and zinc — as well as numerous organic cations. DTX-699 (8:40-43); Tr. 726:19-727:4. The Chucholowski patent also defines pharmaceutically acceptable salt using the open-ended phrase "and the like," to include within its parameters even more salts than those it expressly identified. *Id*.

Dr. Heathcock testified that the Chucholowski patent would also be of further significance to a person of ordinary skill in the art because the assignee, Warner-Lambert, was considered an up-and-coming statin research company at the time. DFF ¶ 26. In addition to the Chucholowski patent, Warner-Lambert had obtained a number of statin patents prior to 1991, one of which covered a compound known to be performing well in trials. Tr. 727:5-728:6, 738:6-739:7. That compound, later known as Lipitor®, eventually became not only the best-selling statin of all time, but also the best-selling drug in the world. Tr. 128:9-19. The Lipitor® patent taught that zinc could be used as a possible statin salt, in addition to other salts outside Plaintiffs' definition. Tr. 738:6-739:7; DTX-688 (7:7-10). Other Warner-Lambert statin patents available prior to the '314 patent also claimed pharmaceutically acceptable salts that were defined to expressly include zinc. Tr. 738:6-739:7; DTX-693 (11:51-54), DTX-694 (9:65-68).

Dr. Heathcock also testified about Sankyo, the true pioneering statin research company. DFF ¶ 27. Sankyo discovered the very first statin in history, compactin, which was the first molecule to reduce cholesterol by inhibiting HMG-CoA reductase. Tr. 732:11-733:11, 747:12-750:20. Although Sankyo was unable to ultimately commercialize compactin, they were eventually successful in bringing another statin, known as pravastatin, to market. Tr. 732:11-733:11. By the late 1980s, Sankyo had also obtained two patents that disclosed statin salts

including not only some of the same salts as Plaintiffs, but dozens of additional salts falling outside of Plaintiffs' definition, including zinc. Tr. 732:17-736:11; DTX-689 (3:25-32, 5:42-6:36), DTX-692 (7:1-9, 7:38-60). While providing an express listing of numerous salts, Sankyo nevertheless left its exemplary list of salts open-ended and non-limiting. *Id*.

Demonstrating Sankyo's serious consideration of zinc statin salts, Sankyo's patents expressly called for zinc in the claim language itself. Tr. 734:22-755:7, 736:6-12; DTX-689 (18:1-28), DTX-692 (31:25-29). Indeed, the effort to claim zinc was deliberate and important, as zinc statin salts were targeted for express patent protection despite the broad, open-ended list of salts disclosed in Sankyo's patent specifications. Tr. 734:22-735:5, 736:5-11; DTX-689 (18:1-28), DTX-692 (31:25-29).

Dr. Heathcock also identified a statin patent by Asahi that expressly disclosed and claimed zinc statin salts and other cations beyond the '314 patent's definition. Tr. 736:12-738:5; DTX-690 (2:50-55, 5:20-6:40, 13:25-40, 15:54-61, 17:16-36). The Asahi patent not only included working examples of aluminum statin salts falling outside Plaintiffs' limited definition, it also disclosed that *in vivo* animal studies had been performed and biological data had been obtained on such aluminum statin salts. Tr. 736:12-738:5; DTX-690 (2:50-55, 5:20-6:40, 13:25-40, 15:54-61, 17:16-36). This provides further evidence that persons of ordinary skill in the art gave serious consideration to statin salts beyond those defined in the '314 patent. The record at trial also evidenced non-patent literature disclosing such salt-forming ions, including zinc, for pharmaceuticals that had been made prior to the filing of the '314 patent. Tr. 739:8-741:8; DTX-684, DTX-685.

3. Plaintiffs Are Barred From Asserting The Doctrine Of Equivalents In Light Of Plaintiffs' Narrowing Definition That Excluded Zinc And Other Known Alternatives From The Broad Plain Meaning Of Their Claims

As shown above, Dr. Heathcock established that by the time Plaintiffs filed the '314 patent some 15 years after the first statin was discovered in 1976, numerous leading statin research companies had disclosed and claimed a vast array of statin salts, including zinc statin salts. DFF ¶ 30. Moreover, there was no suggestion at trial that these references constituted the entire universe of prior art disclosing and claiming zinc statin salts. DFF ¶ 29. Against this backdrop of prior art, Dr. Heathcock testified that a person of ordinary skill in the art would immediately recognize that there are many additional salts that could be made with a statin outside the closed subset that Plaintiffs carved out of its broad, open-ended claim term. Tr. 706:8-20, 717:7-718:16, 719:1-720:7, 755:17-756:16.

Dr. Heathcock testified that such a person would view those ions, such as zinc, not only as foreseeable, but actually having already been foreseen and claimed by the prior art patentees. Tr. 723:22-724:5, 728:7-15, 746:15-747:11, 755:17-756:16. Based on his first-hand experience in the statin field at the relevant time, Dr. Heathcock concluded that the person of ordinary skill in the art would view the possible and foreseeable statin salts falling outside that narrow and finite subset of claimed salts as being excluded from the scope of the '314 patent. *Id*. Dr. Heathcock's conclusions are buttressed by his incomparable expertise in this case regarding the state of the statin art as it existed when the '314 patent was filed in 1991, both in terms of his pedigree and his direct experience in the statin field in the relevant time. DFF ¶¶ 8-10.

Plaintiffs' closed special definition of only a small subset of pharmaceutically acceptable salts by itself establishes the kind of "narrow" claiming required by *Wrigley*. In fact, Plaintiffs'

decision to carve out so many salt-forming ions actually taught in the art of statins far exceeds the *Wrigley* standard.

As in *Sage*, *Freedman* and *Wrigley*, this is not a case in which the patentee's ability to capture the essence of his invention was impeded by linguistic subtlety, obfuscating technical complexity, or the inability to foresee the subsequent development of the alleged equivalent. *Sage*, 126 F.3d at 1425; *Freedman*, 420 F.3d at 1362; *Wrigley*, 683 F.3d at 1359, 1365-66. No language barriers stood in the way of Plaintiffs describing and claiming a broader range of salts. Plainly, Plaintiffs knew how to do so — such a practice was routine for the leading statin companies at the time, and Shionogi itself had done so before when claiming salts in its other pharmaceutical inventions. DFF ¶ 21.

Moreover, again as in *Sage*, *Freedman* and *Wrigley*, the alleged equivalent here is not the product of some unforeseen subsequent technological development in the art. *Sage*, 126 F.3d at 1425; *Freedman*, 420 F.3d at 1362; *Wrigley*, 683 F.3d at 1359, 1366. Rather, as detailed above, zinc was known at the time as a potential alternative that was disclosed and claimed in numerous patents obtained by the leading statin research companies who preceded Plaintiffs in the statin field. DFF ¶¶ 16-18, 30-31. And, although not essential as a matter of law, there can be no genuine dispute that Plaintiffs knew this at the time of their application. The '314 patent inventors, who averred under oath to the PTO that they had reviewed and understood the patent specification, cited the Zocor® Patent in the specification that taught the potential use of zinc as a statin salt. DTX-741 at 5, 32-33. Thus, this case is unlike *Abraxis,* cited by Plaintiffs, where the alleged equivalent "DTPA" compound had been unknown and unforeseeable as a substitute at the time. Br. at 35-36; *Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc*., 467 F.3d 1370,

1381-82 (Fed. Cir. 2006) ("In fact, the absence of known interchangeability underscores that the patent applicant had no reason to foresee and claim DTPA in this combination.").

In this case, the trial record demonstrates that the narrowness of Plaintiffs' chosen special definition also would support a finding of implicit exclusion under *AstraZeneca*, 384 F.3d at 1340. Both in this case and in *AstraZeneca*, the patentee chose to act as its own lexicographer to limit a known group of chemical compounds to a finite subset. And in each case, the prior art reflected that the alleged equivalent came within the larger group of the claim language, but was excluded from the chosen finite subset of the patentee's definition. Moreover, like the patentee in *Wrigley*, Plaintiffs argue here that any kind of exclusion requires the inventor to have criticized the alleged equivalent, or for the alleged equivalent to in some sense be the opposite or antithesis of the claimed element. Br. at 41-43. However, the Federal Circuit rejected the suggestion that "clear disavowal requires an 'expression of manifest exclusion or restriction' in the form of 'my invention does not include _____.'" *AstraZeneca*, 384 F.3d at 1340. Indeed, the Federal Circuit in *AstraZeneca* expressly found that "[t]he inventors' lexicography *alone* works an implicit disavowal . . . ." *Id.* at 1340 (emphasis added).

4. Plaintiffs' Arguments Against The Application Of *Sage* And *Wrigley* Should Be Rejected

Plaintiffs' Brief is essentially a scattershot of fact and legal arguments why *Sage* and *Wrigley* should not apply. None of Plaintiffs' arguments has merit.

a. Plaintiffs' effort to distinguish *Sage* and *Wrigley* fails for the same reasons it failed on summary judgment

As they did on summary judgment, Plaintiffs once again argue that *Sage* and *Wrigley* are distinguishable and thus irrelevant. However, this Court previously considered and rejected Plaintiffs' arguments against application of *Sage* and *Wrigley*, finding them relevant to this case.

D.I. [373] at 9. Plaintiffs' *de facto* attempt to have this Court reconsider its decision should be rejected for the same reasons.[1]

For instance, *Sage* and *Wrigley* are not distinguishable as applying solely to cases of "simple" technology. Br. at 36, 39. Nothing supports Plaintiffs' characterization that the subject matter at issue in *Wrigley* was "simple," and the *Wrigley* court never referred to it as such or even indicated that application of the doctrine of equivalents turned on such characterizations.[2] Br. at 36. Indeed, in precluding application of the doctrine of equivalents over arguments that *Sage* should be limited to simple mechanical cases, the Federal Circuit in *Wrigley* applied the analysis to chemical compounds. *See Wrigley*, 683 F.3d at 1366.

Moreover, in light of the *Wrigley* court's reliance on the narrowness of the claims and foreseeability of the alleged equivalent — the same factors compelling the decision in *Sage* — the suggestion that *Sage* has been "narrowly construed" fails. Br. at 40. None of the cases that allegedly confine *Sage* apply here, where a patentee specifically defined its otherwise broad claim language to be limited to a specific subset of elements that excluded foreseeable alternatives. *Id*. (citing *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005 (Fed. Cir. 2006); *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349 (Fed. Cir. 2012); *Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 149 F.3d 1309 (Fed. Cir. 1998)).

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[1] Plaintiffs do not even attempt to meet the rigorous requirements for reconsideration, as confirmed by this Court in *Yarger v. ING Bank, fsb*, C.A. No. 11-154-LPS, 2012 WL 6062021, at *1 (D. Del. Oct. 9, 2012) (setting standards and required proofs for reconsideration).

[2] Amplifying on this theme, Plaintiffs suggest that *Wrigley* is distinguishable from *Abraxis* based on the alleged predictability of the subject matter. Br. at 36. Contrary to Plaintiffs' suggestion, however, the *Wrigley* court distinguished *Abraxis* not on any alleged predictability of the technology at issue but because, unlike here, it was unknown that the alleged alternative was a "suitable substitute" for the claimed invention. *Wrigley*, 683 F.3d at 1366.

For these reasons as well as those previously offered in summary judgment, the justification for applying the doctrine of equivalents does not exist in this case. If Plaintiffs had desired to broadly protect all pharmaceutically acceptable salts, the language for doing so was not only available, it already existed in the claim language itself. Moreover, had Plaintiffs not so restricted that plain meaning and its claim scope, the PTO could have considered whether such an expanded class of salt forms met the statutory requirements for patentability. *Sage*, 126 F.3d at 1425. Instead, Plaintiffs "left the PTO with manifestly limited claims that it now seeks to expand through the doctrine of equivalents."[3] *Id*. There is no justification for giving Plaintiffs access to the doctrine of equivalents, and the public was entitled to rely on Plaintiffs' express definition that excluded zinc and other commonly understood pharmaceutically acceptable salts.

b. Plaintiffs' asserted "broad" claiming is based on a disregard of all the unclaimed salt-forming ions taught in the prior art

Plaintiffs ignore the majority of unclaimed salt-forming ions taught in the prior art, declaring their claim "broad" when compared to what they call the "real alternatives" of "useable metal salts" of the prior art.[4] Br. at 25-27. Plaintiffs arrive at their tiny universe by redefining

[3] While Plaintiffs argue that this particular harm referenced in *Sage* is not at issue here (Br. at 40), Watson notes that such an allegation would seem to be at odds with Plaintiffs' numerous suggestions throughout their Brief, if they are to be believed, that Plaintiffs had no patentable support for broader claims encompassing zinc because the inventors never made a zinc salt, and forming such a salt was allegedly "unpredictable." *See, e.g.*, Br. at 23-25, 38. In any event, *Sage* makes clear that the cost of Plaintiffs' choices in claim drafting properly fall on Plaintiffs. *See infra* (II)(B)(1)-(2).

[4] In an attempt to legitimize this arbitrary subset of salt-forming ions, Plaintiffs incorrectly assert that Watson is also basing its case on the same limited universe of "useable metal salts." *See, e.g.*, Br. at 25, 26. On the contrary, Watson's argument that Plaintiffs narrowly claimed the salts of the invention is based on the plain words of their chosen definition, as well as the vast number of unclaimed alternative salt-forming ions known to persons of ordinary skill.

the prior art of salt-forming ions by way of two arbitrary restrictions. Not surprisingly, the "useable metal salts" that remain are confined to alkali and alkaline earth metals.

First, without offering any justification, Plaintiffs simply ignore all non-metal salt-forming ions, which constitute a majority of prior art ions outside the scope of the special definition. Br. at 25-27; *see generally* DFF ¶¶ 34-37. The patent itself, however, does not confine the invention to metal ions, but expressly includes a non-metal ion — unsubstituted ammonium. DTX-676 (2:16-21). Moreover, Plaintiffs' expert Dr. Roush failed to offer any purported scientific justification for eliminating non-metal ions, and the working examples of such ions, from consideration. DFF ¶¶ 35-36. Indeed, he admitted that in his own analysis, he had considered such ions, but "chose not to present it" at trial. *Id*.

Also absent is any explanation for why the type of ion used by Watson today bears on the scope of the invention claimed in the patent. Br. at 27. Plaintiffs even hazard a suggestion that the Court itself precluded consideration of non-metal ions in its claim construction ruling. *Id*. Again, however, there is no explanation for why the Court's observation that the scope of non-metal ions in Plaintiffs' definition is a "close question" would cause the person of ordinary skill to disregard all non-metal ions. *Id*.

Regardless, even in Plaintiffs' arbitrary world of only metal ions, Plaintiffs' chosen subset of claimed salts was still narrow, as Plaintiffs' definition still accounted for less than half of the metal cations taught in the prior art. DFF ¶ 37. Moreover, as Dr. Heathcock testified at trial, even disregarding non-metal salts, a person of ordinary skill in the art would still consider those known metal salts falling outside Plaintiffs' limited definition to have been excluded from their invention. Tr. 777:8-19.

Second, Plaintiffs improperly disregard all prior art disclosures and claims except for the working examples. Br. at 30-31; *see generally* DFF ¶¶ 38-42. However, Dr. Heathcock testified that in his experience, companies often do make compounds and disclose them by name without actually describing them in working examples. Tr. 774:14-19. Dr. Heathcock also testified that a company's disclosure of a zinc compound in the patent indicates that the inventors were aware of the fact that zinc salts could be made. Tr. 725:6-9. Plaintiffs' experts offered no contrary evidence. Moreover, Dr. Heathcock could think of no reason why a person of ordinary skill in the art would disregard or ignore the possibility of making a zinc statin because of the absence of working examples. Tr. 725:14-19. In addition, Plaintiffs' consideration of only working examples is squarely at odds with their decision to completely ignore working examples of non-metal ions in the prior art. DFF ¶¶ 35-36.

c. <u>Salt formation was not so unpredictable as to render zinc and the other unclaimed ions unforeseeable</u>

Watson's expert Dr. Heathcock confirmed that a person of ordinary skill in the art at the time would have considered zinc statins foreseen, and would have readily known how to prepare zinc salts of statins despite the absence of working examples. *See generally* DFF ¶¶ 39-42. Dr. Heathcock explained that statins are carboxylic acids, and that chemists are very familiar with the chemistry of carboxylic acids. *Id.*; Tr. 723:22-724:5, 746:15-747:11.

Expounding on this opinion, Dr. Heathcock testified that zinc salts are not unusual. Tr. 723:22-724:5, 746:15-747:11. Examples of well-known zinc salts are zinc benzoate or zinc acetate, both of which are very common. *Id*. Dr. Heathcock also testified that although statins themselves are complicated acids, all chemists would have been able to make a zinc salt of a statin because the process consists of simply mixing a base with the acid. *Id*. Dr. Heathcock further testified that he was not aware of anything indicating that one could not make a zinc salt

of a statin. Tr. 725:10-13. Dr. Heathcock explained that the basic reaction of carboxylic acids is forming salts, and chemists would have not been surprised that you can form various salts beyond those identified in Plaintiffs' limited definition. *Id.* Corroborating Dr. Heathcock's testimony, evidence at trial revealed that Bristol-Myers Squibb was using and experimenting with zinc statin salts at least as early as 1992. DFF ¶ 42.

In contrast to the robust testimony of the predictability of zinc salt formation, Plaintiffs offer no testimony from their own experts endorsing the specific contention that forming a zinc statin salt (regardless of crystallinity) was unpredictable. Br. at 23-24. On the contrary, Plaintiffs' expert Dr. Roush admitted on cross-examination that a person of ordinary skill in 1991 would have been aware that zinc could be used in pharmaceuticals in general, and that with regard to zinc statins specifically, "if you asked a person of ordinary skill, 'do you think you could make a statin as a zinc salt,' they would say – I think they'd say, yes, probably." Tr. 619:18-620:5; DFF ¶¶ 46-47.

The testimony Plaintiffs cite relating to the predictability of crystalline salt forms does not alter this conclusion. Br. at 23-24; DFF ¶¶ 48-49. Indeed, as Plaintiffs' expert Dr. Bugay acknowledged, people of ordinary skill would have expected to readily achieve salt formation generally even if they could not have expected to successfully achieve crystallization of those salts. Tr. 425:24-426:20. Dr. Morris's acknowledgement in his expert report that in chemistry there are no 100% guarantees for salt formation provides no help either. Br. at 23. Dr. Morris made clear that the mechanics of preparing a salt of a carboxylic acid are straight forward and not complicated. Tr. 912:15-913:24. Dr. Morris explained that, despite the lack of absolute predictability in chemistry, one would have a high confidence of making a salt of a carboxylic acid. *Id.* Indeed, salt formation has been described in the pharmaceutical literature as "one of

the simplest chemical reactions" — evidence consistent with Dr. Heathcock's and Dr. Roush's testimony discussed *supra* that a person of ordinary skill in the art would have readily known how to prepare a zinc salt of a statin in 1991. DTX-685 at 6.

Moreover, the Federal Circuit has already rejected the argument that new salts are unknown or would be ignored simply because one of skill is not able to predict with 100% certainty the properties of the new salt, or whether it will form. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1363, 1366 (Fed. Cir. 2007). In rejecting this argument in *Pfizer*, the Federal Circuit explained that those of skill in the pharmaceutical industry in 1986 would readily consider and make other salts of their active ingredient using the same counterions in salts that have already been approved by the FDA, referring to these yet unmade salts as "known." *Id.* at 1362. Notably, this holding was not the Federal Circuit "revers[ing] course," in contrast to Plaintiffs' mischaracterization. *See* Br. at 24. While it appears that one district court may have mistakenly agreed with Plaintiffs' misguided argument about the implications of lack of precise predictability (*Pfizer,* 480 F.3d at 1364), there is no indication that the Federal Circuit has ever agreed with it.[5]

Thus, Plaintiffs' attorney argument that zinc and the other unclaimed salt-forming ions were not foreseeable because they were allegedly "unpredictable" fails. Br. at 23-25.

[5] It is also noteworthy that the Federal Circuit in *Pfizer*, relying on the same Berge reference of record here (DTX-684), specifically found that a person of skill in the pharmaceutical industry would have known of a salt made using one of the 53 anions in salts already approved by the FDA — an anion that was used in only 0.25% of the drugs at the time. *Pfizer*, 480 F.3d at 1363. Here, in contrast, looking at the same Berge reference, zinc is one of only 14 cations and is listed as used in 2.95% of FDA-approved salts at the time. DTX-684 at 2.

d. Foreseeability is determined by the scientific art, and not Plaintiffs' arbitrary construct of the alleged "real world"

Plaintiffs' declaration that zinc was not foreseeable because it was not a "real alternative" also fails. Br. at 28-33. *Wrigley* squarely refutes the proposition that the foreseeability of an alleged equivalent depends on whether it is proven to be commercially viable on the consumer market, or what consideration an inventor gave to using the alleged alternative. *Wrigley*, 683 F.3d at 1359, 1366. Whether the inventor actually tried the alleged alternative, or considered it to be commercially viable, is irrelevant in view of an alternative's potential interchangeability. *Wrigley*, 683 F.3d at 1366. Thus, Plaintiffs' arguments about Shionogi's failure to consider zinc at the time, AstraZeneca's subsequent classification of zinc as a "class 3" salt, and literature surveys of what salts were contained in commercial drug products, have no bearing on foreseeability in the prior art. Br. at 29-30.

Plaintiffs also attempt to denigrate the true pioneering statin work done by their competitors Merck, Sankyo and Warner-Lambert, as reflected in their numerous prior art statin patents filed years before the '314 patent. Br. at 30-31. Plaintiffs dismiss zinc and other ions disclosed and claimed therein as "speculative" and "bizarre" based on Plaintiffs' failed argument about lack of working examples and commercial use.[6] *Id.* Notably, while Plaintiffs disparage the prior art disclosures for lack of working examples or evidence of commercial use, the '314 patent itself expressly names and claims salts such as lithium, cesium, beryllium, and magnesium, which similarly fail to make Plaintiffs' list of exemplified "real world" salts. DFF ¶ 43; PPFF ¶¶ 41-43.

[6] Plaintiffs also attempt to dismiss Shionogi patents, which generically claim zinc, for not mentioning the cation by name. However, consistent with the many prior art statin patents teaching the use of zinc prior to 1991, Shionogi did expressly identify zinc as a potential salt-forming cation in another pharmaceutical patent. Br. at 30 n.2; DTX-707 (6:32-34).

Moreover, as a matter of law, the prior claimed zinc statin salt inventions that Plaintiffs simply declare "speculative" presumptively meet both the enablement and written description requirements for patentability. *See* 35 U.S.C. § 282(a) ("A patent shall be presumed valid."). Conclusory adjectives are no substitute for the requisite clear and convincing evidence to the contrary. Nor is Plaintiffs' citation to *In re Oelrich*, 579 F.2d 86, 91 (C.C.P.A. 1978). Br. at 30-31. *In re Oelrich* did not address the foreseeability of an equivalent in a prior art patent. Rather, it dealt with the different question of whether a statement from a single prior-art patent rendered the invention at issue obvious. *Oelrich*, 579 F.2d at 91.

Finally, while Plaintiffs argue that Egis treated rosuvastatin as unforeseeable in prosecuting patent applications, none of the citations Plaintiffs offer in support of their allegation state that Egis thought that rosuvastatin zinc was "unforeseeable." Br. at 31-32. Nor do they assert that a person of ordinary skill would not have considered zinc to be a potential salt of a statin in 1991. *Id*. Moreover, while Egis may ultimately prevail on these arguments, such as by evidencing unexpected results sufficient to overcome an obviousness rejection, the specific arguments Plaintiffs point to were rejected by various patent offices, and no patent has issued on the zinc salt. PTX-1301 at 854-856, PTX-1302 at 1-11. In any event, these statements are immaterial because the potential suitability of zinc cations in the field of statins was indisputably disclosed in the prior art, and thus foreseeable, as discussed above.[7]

[7] Plaintiffs also assert that "Watson should not now be heard to allege a contrary state of fact as to the foreseeability of rosuvastatin zinc . . .", as though Egis's prosecution statements are somehow attributable to Watson. Br. at 31. Plaintiffs also offer no authority for such a novel legal proposition. Moreover, Egis is a separate company, and Plaintiffs have not even attempted to establish that Watson has control over Egis's patent applications.

e. Plaintiffs misstate the law and Watson's position on the role of foreseeability

In presenting their legal arguments, Plaintiffs either misconstrue or attempt to obfuscate Watson's arguments. For example, Watson is not arguing that foreseeability alone prevents access to the doctrine of equivalents. Br. at 33 (citing *Graver Tank* and *Warner-Jenkinson*). Instead, as Watson has articulated elsewhere, foreseeability bars access to the doctrine of equivalents in conjunction with the very specific circumstances that exist here — namely, where a patentee deliberately carves out a subset of possible alternatives from their broad claim language, and where there was no shortcoming in language or advance in technology that prevented the patentee from including the alternatives in their claim scope. While cases such as *Sage* and *Wrigley* address these circumstances, *Graver Tank* and *Warner-Jenkinson* do not. Br. at 33.

Moreover, despite admitting to the Court during closing argument that foreseeability is a "factor" to be considered in this case, Plaintiffs now urge the Court to find that foreseeability is limited to cases of prosecution history estoppel. *Compare* Tr. 1177:4-18 *with* Br. at 34-36. Regardless, while prosecution history estoppel cases examine the rationale for assessing foreseeability in view of drafting decisions made during prosecution, *Sage* and its progeny articulate the rationale for doing so in view of drafting decisions made at the time of the application.

Indeed, this is not a "very different" situation, as Plaintiffs suggest in citing *Warner-Jenkinson*. Br. at 20, 34. The "very different" situation there alludes to a hypothetical situation in which a patentee were to present the narrower language in the original claims. *Warner-Jenkinson*, 520 U.S. at 30-31 (citing *Exhibit Supply Co. v. Ace Patents Corp.*, 315 U.S. 126, 136

(1942)).[8] Here, in contrast, there is no dispute that Shionogi included the broader "pharmaceutically acceptable salt" term in its original claims. Accordingly, the policy considerations barring the doctrine of equivalents here are in accord with those underlying file history estoppel. Indeed, as the Supreme Court in *Exhibit Supply* makes clear, such a change or amendment shows that the patentee "recognized and emphasized the difference between the two phrases and proclaimed his abandonment of all that is embraced in that difference." *Exhibit Supply*, 315 U.S. at 136. That this proclamation was made in the initial application rather than a later time during prosecution is irrelevant. In both cases, the public is made aware of and entitled to rely on the expressly-abandoned claim scope.

Moreover, Watson's position does not "reduce" to a repeat analysis of literal infringement. Br. at 22. While literal infringement is based on claim construction and what a claim means, access to the doctrine of equivalents is based on whether a patentee is entitled to go beyond what a claim means. Here, the lexicographic definition alone resolves the literal infringement analysis. The equivalence analysis, however, goes further and assesses that narrow definition in view of the original broad claim language that covered known, foreseeable alternatives that were excluded by the narrow definition. This assessment is not a mere repeat of the Court's claim construction analysis, as Plaintiffs allege. Br. at 21-22. Indeed, if it were true that assessing the circumstances surrounding a patentee's narrow claiming was tantamount to a repeat claim construction analysis, cases like *Sage* and *Wrigley* would not have been so decided.

Ethicon, 149 F.3d 1309, and *Deere*, 703 F.3d 1349, are inapposite. Br. at 22. Neither *Ethicon* nor *Deere* involves the situation where a patentee seeks to recapture broad claim

[8] Watson notes that even in the "very different" situation referred to there, the Supreme Court treats access to the doctrine of equivalents as not guaranteed, and was only "assuming" its application for purposes of its analysis. *Exhibit Supply*, 315 U.S. at 136.

language through the doctrine of equivalents, despite having expressly defined it to cover only a limited subset of elements that excluded the foreseeable equivalent. *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151 (Fed. Cir. 2012), and *U.S. Phillips Corp. v. Iwasaki Elec. Co.*, 505 F.3d 1371 (Fed. Cir. 2007), are also irrelevant. Br. at 21-22. *Pozen* and *U.S. Phillips* are numerical range cases belonging to the Federal Circuit's extensive jurisprudence on the application of the doctrine of equivalents to claims expressed as numerical ranges, often introduced or qualified by phrases like "at least," "approximately" or "less than." *Pozen*, 696 F.3d at 1170-71; *U.S. Philips*, 505 F.3d at 1378 (numerical ranges subject to doctrine of equivalents). According to the Federal Circuit, the distinction between numerical range claim terms and non-numerical claim terms is significant. *See U.S. Philips*, 505 F.3d at 1378-79 (in doctrine of equivalents analysis, distinguishing case law dealing with non-numerical claim terms from case law dealing with numerical range claim terms).

Finally, Watson is not contending that "Plaintiffs should have disclosed the invention more broadly." Br. at 22-23. This argument is simply pretext for Plaintiffs' hindsight rationalization for unnecessarily narrowing their claim language. Plaintiffs suggest that they narrowly defined their invention because not doing so would have rendered their claims invalid under *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352 (Fed. Cir. 2007) and *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Br. at 23. This rationalization ignores the fact that Plaintiffs already defined their claims to cover more metal salts than the two they had made and described — calcium and sodium. Plaintiffs offer no evidence for the contention that making two salts was sufficient to overcome these alleged concerns with enablement and unpredictability as to the remaining claimed metal salts. *See* Br. at 25. Moreover, Plaintiffs defined their claims to cover unsubstituted ammonium despite never having made an unsubstituted ammonium salt of

rosuvastatin (or any substituted ammonium salt of rosuvastatin) before filing the '314 patent. Plaintiffs' suggestion that they were merely at the mercy of "unpredictability" or strict claim drafting rules in abandoning the plain meaning rings hollow. *See* Br. at 25.

B. Public Policy And Equitable Considerations Favor Watson

In the absence of any legal precedent to save them from their own claiming strategy, Plaintiffs ask the Court to do so as a matter of "equity." This is putting the cart before the horse. For the reasons set forth above, Plaintiffs are legally precluded from asserting the equitable doctrine of equivalents. That is, Plaintiffs do not have the legal right to raise any equitable arguments.

But even if Plaintiffs were not barred from making their equitable arguments, the public policy and equitable considerations against allowing Plaintiffs' requested range of equivalents far outweigh Plaintiffs' proffered equitable considerations, which are not recognized as controlling.

1. The Doctrine Of Equivalents Cannot Rectify "Naïveté" In Drafting As A Matter Of Law

In response to a question from the Court in closing, Plaintiffs speculated that their decision to narrowly define the claimed salts was a product of "inarticulate drafting" and "perhaps naïve drafting." Tr. 1179:15-21. Plaintiffs also suggested that it seemed unfair for their intellectual property rights to be compromised by virtue of a drafting technicality. *Id.*; Tr. 1175:20-1176:2, 1179:4-9. Plaintiffs contemplate that the Court should consider this in deciding whether it is "fair and reasonable" to enforce the patent, as a matter of "equity." *Id.*; Br. at 48-49.

As a matter of law and public policy, however, the Federal Circuit has already determined that the cost of "naïve" or "inarticulate" drafting decisions is properly imposed on the

patentee instead of the public. As the court explained in *Sage,* the cost to an individual patentee is far outweighed by the societal cost of chilled competition produced by a rule to the contrary:

> This court recognizes that such reasoning places a premium on forethought in patent drafting. Indeed this premium may lead to higher costs of prosecution. However, the alternative rule—allowing broad play for the doctrine of equivalents to encompass foreseeable variations, not just of a claim element, but of a patent claim—also leads to higher costs. Society at large would bear these latter costs in the form of virtual foreclosure of competitive activity within the penumbra of each issued patent claim. Because the doctrine of equivalents blurs the line of demarcation between infringing and non-infringing activity, it creates a zone of uncertainty, into which competitors tread only at their peril. Given a choice of imposing the higher costs of careful prosecution on patentees, or imposing the costs of foreclosed business activity on the public at large, this court believes the costs are properly imposed on the group best positioned to determine whether or not a particular invention warrants investment at a higher level, that is, the patentees.

Sage, 126 F.3d at 1425 (internal citation omitted). Thus, the Court should not give any consideration to Plaintiffs' direct and indirect arguments as to the fairness of this case in light of what Plaintiffs assert was merely "naïve" or "inarticulate" drafting.

2. Public Policy And Equities Weigh Against Allowing Plaintiffs' Asserted Range Of Equivalents

As a matter of policy and fairness, when the public sees that an applicant expressly defines a term narrower than its ordinary meaning, the public should be entitled to rely on the public notice function — at least not to allow the applicant to reclaim precisely the ordinary meaning that the applicant eschewed by his definition. Otherwise, special definitions provided by applicants would have no practical meaning or effect. While the claim terms themselves would remain, their definitions would be eviscerated from the patent.

As Plaintiffs' own citation to *Graver Tank* makes clear, the true purpose of the doctrine of equivalents is to protect the inventor from being "at the mercy of verbalism." Br. at 45 (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods., Co.*, 339 U.S. 605, 607 (1950)). Here,

Plaintiffs were not at the mercy of verbalism. Plaintiffs had already drafted claims that covered the alleged equivalent and could have sought to enforce that broad claim scope if they had only refrained from publicly opting out of that claim language and narrowly redefining it to exclude foreseeable alternatives.

While the equitable principles underlying the doctrine of equivalents act as a shield to protect patentees from the limitations inherent in language, they cannot operate as a sword to capture foreseeable alternatives excluded by deliberate claiming choices. This, however, is exactly what Plaintiffs seek to do here. Having excluded various salts such as zinc from the scope of Claim 6, Plaintiffs seek to misappropriate the doctrine of equivalents to reclaim the plain meaning of the term they specifically redefined — as though they had never done so. Indeed, Plaintiffs' experts all confirmed that their tests for equivalence were met because the accused rosuvastatin zinc product satisfied the ordinary meaning of the term "pharmaceutically acceptable salt." DFF ¶¶ 51-54. For example, Plaintiffs' expert Dr. Bugay confirmed that his test for equivalence was simply whether or not the salt is non-toxic and can deliver the rosuvastatin anion to the patient. Tr. 441:2-9, 442:18-24. Thus, Plaintiffs' theory of infringement under the doctrine of equivalents improperly transforms the specifically-defined and narrowly-focused claim term "pharmaceutically acceptable salt" into a functional abstract, unrestricted by the lexicographic definition set forth by Plaintiffs in the specification. *Sage*, 126 F.3d at 1424.

Moreover, in circumstances akin to the present case, the Federal Circuit has determined there to be no equivalence where a patentee attempts to recapture through the doctrine of equivalents the full scope of a narrowed claim. *See, e.g., Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1160 (Fed. Cir. 1998); *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.,* 541 F.3d 1115, 1128-

29 (Fed. Cir. 2008). The Federal Circuit in *Tronzo* and *Carnegie* precluded as a matter of law reliance on the doctrine of equivalents where the patentee's test for equivalence for a limitation in a narrower, dependent claim would recapture all the embodiments covered by the broader claim from which it depended. *Tronzo*, 156 F.3d at 1160; *Carnegie*, 541 F.3d at 1128-29. The court reasoned that permitting such a recapture would violate the "all limitations rule" and vitiate the narrowed limitation. *Id*.; *see also Durel Corp. v. Osram Sylvania, Inc.*, 256 F.3d 1298, 1304-05 (Fed. Cir. 2001) (finding vitiation where the accused device falls outside of the patentee's specific definition).

3. Plaintiffs' Other Equitable Arguments Are Irrelevant

Plaintiffs argue that the Court should consider factors such as "medical importance," the alleged "risks" of infringement, or whether enforcement of the '314 patent is "fair and reasonable." Br. at 46-49. The petitioner in *Warner-Jenkinson* made a similar argument as Plaintiffs do here. *Warner-Jenkinson*, 520 U.S. at 34 ("Relying on *Graver Tank's* references to the problem of an 'unscrupulous copyist' and 'piracy,' petitioner would require judicial exploration of the equities of a case before allowing application of the doctrine of equivalents.") (internal citation omitted). The Supreme Court rejected this notion as in conflict with "the objective approach to infringement." *Id*. at 35-36.

The Supreme Court established that the "equities" of infringement under the doctrine of equivalents are not to be taken into consideration any more than they would be with literal infringement. *Id*. at 35. Even with regard to the issues of the "unscrupulous copyist" and "piracy," as discussed in *Graver Tank* and quoted by Plaintiffs, those two issues are not in play here despite Plaintiffs' allegation that Watson and Egis "recognized the risk of infringement," and "are not innovators." Br. at 45, 47-48.

First, the accused rosuvastatin zinc product is not a copy or piracy. Rather, Egis chemists chose to investigate a zinc salt of rosuvastatin because zinc, as a transition metal, has a higher coordination ability and higher electron density than alkali and alkaline earth metals, likely resulting in a more stable salt. Tr. 521:11-522:17. Egis was subsequently proven right, as their independent research and development culminated in a rosuvastatin salt substantially better than Plaintiffs' optimized rosuvastatin calcium. *See infra* (III).

Second, the patent law itself encourages competing pharmaceutical development, with provisions designed to incentivize products such as Watson's rosuvastatin zinc for the benefit of the public. *See, e.g.*, *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1344 (Fed. Cir. 2007) (quoting 149 Cong. Rec. S15885 (daily ed. Nov. 25, 2003)). Certainly, Plaintiffs do not accuse Congress of passing laws that ratify and encourage "piracy" or "unscrupulous copyists." Rather, Watson's rosuvastatin zinc product, already tentatively approved by the FDA (PPFF ¶ 3), was an outgrowth of the exact developmental efforts endorsed and authorized by Congress.

4. <u>The '314 Patent Is Not A "Pioneer Invention" And Is Not Entitled To Any Range of Equivalents</u>

A pioneering invention constitutes "a distinct step in the progress of the art, distinguished from a mere improvement or perfection of what had gone before." *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 846 F.2d 1369, 1370 (Fed. Cir. 1988) (quoting *Westinghouse v. Boyden Power Brake Co.*, 170 U.S. 537, 562 (1898)). The scope of equivalents accorded a pioneer invention "flows directly from the relative sparseness of prior art in nascent fields of technology." *Id*.

One of the most well-established facts at trial was that by the time the '314 patent application was filed in 1991, the statin art was crowded and well-developed. Tr. 753:16-754:21.

As Plaintiffs' expert Dr. Roush admitted, "[t]he statin field in that period was very competitive. There were many, many companies working on statins . . . ." Tr. 566:13-15. The '314 patent itself describes the statin prior art as consisting of multiple generations by the time of the invention, and rosuvastatin operates by the same key cholesterol-inhibiting mechanism of action common to all prior art statins. DFF ¶¶ 55-57. Moreover, Plaintiffs were forced to seek reissue and narrow their claims in order to evade the strictures of the statin prior art. *Id*. Thus, the '314 patent cannot be considered a pioneer patent. *Id.*

In apparent recognition of the record, Plaintiffs have dropped any pretense of actually satisfying the pioneer invention standard. Br. at 46-47. Undeterred, however, Plaintiffs nevertheless seek to gain the same benefit as a pioneer invention by suggesting a standard that lowers the threshold to a vague assessment of "substantial advancement." Br. at 46-47. In support, Plaintiffs cite *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 63 (1923). *Id*. However, that case has never been applied by the Federal Circuit for the proposition Plaintiffs cite, and Plaintiffs offer no subsequent authority for how this 90-year-old case might apply here, if at all, in view of the more contemporaneous and established line of pioneering invention cases.

Plaintiffs attempt to achieve a broadened scope of equivalents akin to pioneering inventions by relying on an internal AstraZeneca marketing presentation. Br. at 47. However, this data cannot possibly warrant the broad scope of equivalents Plaintiffs seek. DFF ¶¶ 58-59. Indeed, Plaintiffs' own witness called to testify about this data admitted that the primary endpoint of the most recent AstraZeneca study comparing rosuvastatin and atorvastatin showed no statistically significant difference between the two drugs. DFF ¶ 59. He also confirmed that AstraZeneca's own studies show that atorvastatin and rosuvastatin achieve similar results under several metrics. DFF ¶¶ 58-59.

Finally, despite being a "7th in class" statin, and sharing the same core structure as every other statin, Plaintiffs allege that rosuvastatin is not a "me-too" statin. Br. at 47; DFF ¶¶ 55-57. The document Plaintiffs rely on in support of this assertion, however, should be accorded no weight. Plaintiffs' own expert did not testify about the substance of this document, and Watson's expert only confirmed that certain statements were made in it. DFF ¶ 60. The article's substance merely discusses various commercial statins, and notes some structural differences among them. DFF ¶ 60. It certainly does not establish that rosuvastatin operates by a mechanism of action distinct from other statins, or that rosuvastatin is not a "me too" statin — and no expert in this case so testified. *Id.*; Br. at 47.

Crestor's effectiveness in lowering cholesterol, like that of the other commercially-approved statins that followed the discovery of compactin, cannot alone confer the benefit of pioneer status. Tr. 756:17-757:2. Moreover, Plaintiffs offer no authority for the proposition that a pioneer invention, or even a "substantial advancement," would allow them to overcome the legal and public notice consequences of narrow drafting under *Sage* and *Wrigley*.

III. WATSON'S ROSUVASTATIN ZINC SALT IS SUBSTANTIALLY DIFFERENT FROM THE CLAIMED ROSUVASTATIN SALTS

A. The Proper Framework For Assessing Factual Equivalence

1. Legal Standards

To infringe under the doctrine of equivalents, an accused product must contain elements identical or equivalent to each element of the asserted claims. *Warner-Jenkinson*, 520 U.S. at 29. Courts have developed at least two tests for assessing when an element is equivalent. One test is the so-called "insubstantial differences" test, which finds equivalence if nothing more than "insubstantial differences" distinguish the claim element from the corresponding aspects of the accused product. *Warner-Jenkinson*, 520 U.S. at 39-40; *Sage*, 126 F.3d at 1423.

Under the second test, an element in an accused product is equivalent if it performs substantially the same function as the claim element, in substantially the same way, to achieve substantially the same result. *Warner-Jenkinson*, 520 U.S. at 39-40; *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1518 (Fed. Cir. 1995). This framework is commonly called the "function-way-result" or "triple identity" test. *Id.* The function-way-result test has been notably described as a "poor framework" for assessing equivalence in the context of claims to chemical compounds. *Warner-Jenkinson*, 520 U.S. at 39-40.

Regardless which test is used, the equivalence analysis focuses on the role played by each element in the context of the specific patent claim. *Warner-Jenkinson*, 520 U.S. at 39-40. A claim element's role, however, is not defined solely by the express words in the claim. It also depends on factors such as the nature of the invention and the disclosure in the specification. *Viskase Corp. v. American Nat'l Can Co.*, 261 F.3d 1316, 1324 (Fed. Cir. 2001); *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 141 F.3d 1084, 1090 (Fed. Cir. 1998). It is the person of ordinary skill, moreover, who provides the lens through which this equivalence assessment is made. *Lighting World, Inc. v. Birchwood Lighting, Inc.*, 382 F.3d 1354, 1357 (Fed. Cir. 2004) (citing *Hilton Davis*, 62 F.3d at 1518-19).

2. Physical-Chemical Properties Are Central To The Factual Equivalence Analysis

The '314 patent describes and claims rosuvastatin in salt form — not in its anionic or free forms. The reason pharmaceuticals are prepared in salt form is to change or improve the compounds' physical-chemical properties. DTX-685 at 6, DTX-713 at 1, 5; Tr. 911:19-912:14. Because the role of a salt is to change or improve these properties, claiming rosuvastatin in salt form focuses the equivalence analysis on the salts' physical-chemical properties rather than simply how the rosuvastatin ion behaves in the body after the salt dissolves. *See Warner-*

Jenkinson, 520 U.S. at 39-40. Indeed, for those of ordinary skill, comparing and assessing pharmaceutical salts means comparing and assessing them in terms of physical-chemical properties. DTX-685 at 6, DTX-713 at 1, 5; Tr. 908:19-909:16.

Plaintiffs not surprisingly frame a different test for equivalence. To cast the net of infringement as broadly as possible, Plaintiffs suggest the only requirement is a non-toxic salt of rosuvastatin that can get some rosuvastatin into the body. Br. at 6. This retreat to the claim's plain-meaning runs afoul of the legal limitations on, and public policies behind, the doctrine of equivalents, as discussed above. *See supra* (II)(A)(4)(e). But it also fails in view of the facts. Plaintiffs' test is based on the erroneous assumption that the '314 patent is simply a "drug discovery" patent focused solely on the performance of the biologically active agents with no concern for the physical-chemical properties of the salt forms. PPFF ¶¶ 11-13. The problem, again, is that the '314 patent claims rosuvastatin not in its anionic or free forms but rather in salt form. The salt is not simply a "delivery vehicle," as Plaintiffs' contend (PPFF ¶ 26), but is fundamental to the nature and performance of the pharmaceutical compound. DTX-685 at 6, DTX-713 at 1, 5; Tr. 911:19-912:14. Simply requiring something that gets rosuvastatin into the body grossly oversimplifies the equivalence assessment.

In addition to the claims, the rest of the '314 patent also undermines Plaintiffs' characterization and confirms that central to the equivalence analysis is the salts' physical-chemical properties. In describing the preparation of salt compounds, for example, the patent actually reports various salts' physical-chemical properties, and identifies certain salts as "preferred," as Plaintiffs' expert Dr. Bugay acknowledged during cross examination. DTX-491 (7:21-22, 11:22-23, 14:1-3); Tr. 440:9-16, 468:23-470:1. The patent, moreover, describes how the inventors actually made rosuvastatin in *two different* salt forms. *Id*. (9:16-11:40, 13:60-14:8).

Preparing a drug candidate in an extra salt form conflicts with Plaintiffs' characterization of the patent and the inventors as simply focused on synthesizing and identifying a new biologically active agent. *See* PPFF ¶¶ 11-14. Finally, by describing finished dosage formulations for the pharmaceutical agents, as well as methods for administering them to patients, the patent goes beyond mere drug discovery and contemplates development and optimization of physical-chemical properties. DTX-491 (4:15-32); Tr. 899:9-900:18.

More fundamentally, Plaintiffs err in suggesting a division between "drug discovery" and "drug development." PPFF ¶¶ 11-14. In the pharmaceutical industry, these two terms overlap, as Plaintiffs' expert acknowledged during cross examination. Tr. 471:7-472:3, 902:22-903:17. Attempting to relegate an assessment of physical-chemical properties to some later, separate stage in the life of a pharmaceutical candidate — a stage that is conveniently outside the scope of the '314 patent — conflicts with pharmaceutical industry practice and the understanding of persons of ordinary skill. *Id*.

The test for equivalence cannot be watered down to capture any competing rosuvastatin salt that is non-toxic and manages to deliver some rosuvastatin to the body. Rather, equivalence in the context of the '314 patent demands a comparison in terms of physical-chemical properties — the same way a person of ordinary skill compares pharmaceutical salts. Whether assessed independently under the *insubstantial differences* framework, or instead as part of the *function* performed by the salt, the *way* the salt performs the function, or the *result* of the salt, differences

in physical-chemical properties dictate whether an accused rosuvastatin salt infringes the '314 patent claims under the doctrine of equivalents.[9]

3. Three Physical-Chemical Properties Are Particularly Relevant: Chemical Stability, Hygroscopicity, And Crystal Formation And Physical Stability

Three physical-chemical properties are routinely identified by those of ordinary skill as critical when assessing pharmaceutical salts, and are particularly relevant here: (a) chemical stability, (b) hygroscopicity, and (c) ease of crystal formation and physical stability of the resulting crystals. DTX-685 at 6, DTX-713 at 5; Tr. 909:11-912:14, 956:4-957:3.

Chemical stability refers to the tendency of a substance to remain pure and avoid degradation over time. For pharmaceuticals, the need for chemical stability is clear — degradants and impurities can pose significant physical harm to patients. Hygroscopicity refers to the tendency of a substance to take up and hold water. Hygroscopicity is critical because pharmaceuticals demand accurate and precise active ingredient levels, and even a small change in a drug's water content can lead to manufacturing inconsistencies. Variation in water content can also lead to reduced chemical and physical stability. DFF ¶ 65.

The third critical property, ease of crystal formation and physical stability of the crystals, is important because crystalline pharmaceutical materials generally provide several benefits over their amorphous counterparts. These general benefits include easier purification, greater

[9] While the physical-chemical differences are central to the equivalence analysis regardless which test is applied, Watson submits that in the context of the '314 patent the insubstantial differences test is more appropriate than the function-way-result test. Plaintiffs' proposed function-way-result test for the '314 patent, which amounts to nothing more than describing the same "soluble salt" requirement three different ways, only underscores the test's limitations here. Br. at 6. This unhelpful prescription makes particularly applicable here the Supreme Court's comment that the function-way-result test provides a "poor framework" when assessing equivalence in the context of chemical inventions. *See Warner-Jenkinson*, 520 U.S. at 39-40.

stability, defined and reproducible melting points, and improved handling. Preparing pharmaceutical salts in crystalline form also makes it easier to confirm salt formation. Not surprisingly, a substantial majority of AstraZeneca's commercial products were sold in crystalline form. DFF ¶ 66.

But just forming a crystal is not enough – the salt must retain its crystallinity over time. The loss of crystallinity leads to impurities, potentially rendering a pharmaceutical unusable. The tendency of a crystalline compound to retain its crystallinity is called "physical stability." DFF ¶ 67.

Plaintiffs' dismiss these properties as immaterial to the equivalence analysis because the specification and claims fail to expressly list them. Br. at 11. (Ironically, Plaintiffs at the same time appear to elevate as critical to the equivalence analysis other physical-chemical properties, such as solubility and tablet dissolution, despite the lack of an express discussion in the patent. Br. at 7-9, 17.) But Plaintiffs are wrong — there are multiple express descriptions in the '314 patent of crystal formation and the physical stability of the resulting crystalline materials, as their own expert acknowledged during cross examination. Tr. 468:23-470:1. Indeed, some compounds are described as "crystals," while others are described as "powdery crystals," and still others simply as "powdery." DTX-491 (6:24-26, 11:19-23, 13:65-14:1); Tr. 899:9-900:18.

Whether or not expressly described in the patent, an equivalence analysis for claims directed to pharmaceutical salts, like the '314 patent claims, demands a consideration of these physical-chemical properties. Not only are such properties commonly understood by those in the field as critical to assessing pharmaceutical salts, they are fundamental to the role played by the salt claim elements. *See Viskase,* 261 F.3d at 1324; *Vehicular Techs*., 141 F.3d at 1090.

4. AstraZeneca's Alternative Rosuvastatin Salt Investigation Confirms The Importance Of These Physical-Chemical Properties

In studying its amorphous rosuvastatin calcium salt, AstraZeneca identified several physical-chemical shortcomings. Confronted with these limitations, AstraZeneca investigated alternative rosuvastatin salts. The assessment and comparison of these alternative rosuvastatin salts not surprisingly centered on the critical physical-chemical properties of chemical stability, hygroscopicity, and crystal formation and physical stability. DFF ¶ 69. AstraZeneca's investigation confirms that in practice these three physical-chemical properties are central to an assessment of pharmaceutical salts. There is no evidence indicating that the assessment of pharmaceutical salts in the context of the '314 patent should be any different. Rather, the patent, the nature of the invention, and the role played by the salt claim elements compel it. *See supra* (III)(A)(1).

B. Watson's Rosuvastatin Zinc Salt Is Substantially Different From The Claimed Rosuvastatin Calcium Salt

1. Substantial Differences In Chemical Stability

Watson's rosuvastatin zinc salt is substantially more chemically stable than rosuvastatin calcium. AstraZeneca, after years of optimizing the calcium salt of rosuvastatin, prepared several "late development batches" for FDA qualification testing. DFF ¶ 70. The testing revealed a major degradation impurity in the salt, which AstraZeneca labeled the "B2" degradation product. *Id*. The Court heard extensive testimony at trial regarding this impurity.

AstraZeneca was forced to implement special protocols to accommodate rosuvastatin calcium's elevated levels of B2. For example, the specification levels, which refer to the maximum amount of an impurity permitted in an FDA-approved product, were set at many times the normal limits. For its rosuvastatin calcium drug substance (i.e., the bulk active ingredient material), AstraZeneca had to set the specification level at 0.8%, over five times the

identification threshold of 0.15%. DFF ¶ 71. Similarly, for its drug product (i.e., Crestor® tablets), the specification was set at 1.5%, three times the normal limit of 0.5%. *Id*.

Watson's rosuvastatin zinc, on the other hand, consistently shows negligible levels of B2.[10] All qualification batches of Watson's rosuvastatin zinc bulk material showed B2 levels less than 0.03%, well below the 0.15% standard level. DFF ¶ 72. Long-term stability testing, moreover, confirmed that the rosuvastatin zinc bulk material retained these nearly undetectable B2 levels, *even after eighteen months*. *Id*. The B2 specification level for Watson's rosuvastatin zinc bulk material was accordingly set at a nominal 0.1%. *Id*. The negligible B2 levels combined with low levels of the remaining impurities permitted Watson to set the total impurity level for their rosuvastatin zinc bulk material at 1.0%, which is significantly lower than the 1.5% total impurity specification AstraZeneca set for its more mature rosuvastatin calcium bulk material. *Id*.

Even after formulated into a tablet, Watson's zinc rosuvastatin continues to show negligible B2 levels. More specifically, after twelve months under various storage conditions, the level of B2 in Watson's rosuvastatin zinc tablets remains at or below 0.03%, substantially lower than AstraZeneca's optimized rosuvastatin calcium tablets. DFF ¶ 73. That the FDA approved the elevated impurity specifications for Plaintiffs' Crestor® product does not alter the fact that to those in the industry the impurity levels seen in Watson's rosuvastatin zinc are substantially different. *See* Br. at 15.

AstraZeneca's Crestor® formulation further highlights the substantial chemical stability differences between the two salts. AstraZeneca added to its rosuvastatin calcium tablet

[10] By way of terminology, the B2 impurity is referred to in the Egis and Watson regulatory documents as "Impurity 2" or "RVA-IMP 2" when discussing the rosuvastatin zinc bulk material, and as "ROS-3" when discussing the rosuvastatin zinc finished tablets. DFF ¶ 72.

formulation a chemical stabilizer, reporting to the FDA that it was added because of rosuvastatin calcium's tendency to degrade to form the B2 impurity. DFF ¶ 74.[11] This stabilizer, in fact, is the third largest ingredient by mass in the rosuvastatin calcium tablet formulation. *Id*. Watson's rosuvastatin zinc tablets, in contrast, contain no stabilizer; yet still consistently achieve nearly undetectable levels of B2. *Id*.

The B2 impurity was not the only degradation product AstraZeneca had to accommodate in its Crestor® product. AstraZeneca also saw elevated levels of the "rosuvastatin lactone" impurity. DFF ¶ 75. Rosuvastatin lactone admittedly presents a reduced risk compared to the B2 impurity due to its chemical relationship to rosuvastatin. *Id*. AstraZeneca nevertheless had to accommodate these elevated lactone levels by setting the specification at 1.5%, three times the normal limit. *Id*. Indeed, AstraZeneca cited rosuvastatin calcium's tendency to degrade to form the lactone impurity as another reason for adding the chemical stabilizer to its rosuvastatin calcium formulation. DTX-858 at 504.

Watson's tablets show lactone levels well within AstraZeneca's 1.5% specification. In fact, long-term stability tests show that, even in the absence of a stabilizer, the amount of rosuvastatin lactone in Watson's rosuvastatin zinc tablets is less than 1.0%, even after twelve months under various storage conditions. DFF ¶ 76.[12]

Plaintiffs' response to the overwhelming evidence of substantial chemical stability differences is simple deflection. Instead of focusing on the voluminous data from the official,

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[11] In contrast to Plaintiffs' suggestion on page 15 of their Brief, Dr. Morris was not asserting that rosuvastatin calcium required a stabilizer; he was simply repeating AstraZeneca's own admission to the FDA that it was necessary. DTX-858 at 504; Tr. 927:11-928:11.

[12] The rosuvastatin lactone impurity is identified in Watson's regulatory documents as "ROS-1" when referring to the rosuvastatin zinc tablets. DTX-766 at 12.

regulatory testing of its more mature, FDA-approved rosuvastatin calcium, Plaintiffs point to scant data from isolated rosuvastatin calcium batches made by smaller companies — batches that have never been FDA-approved or sold in the United States.

Plaintiffs point, for example, to stability data collected from a single batch of rosuvastatin calcium produced by a company called Glenmark, arguing that it is possible to prepare rosuvastatin calcium with low B2 levels. Br. at 14; PPFF ¶ 132; Tr. 455:14-456:13. Even if Plaintiffs' evidence from these isolated batches was relevant in view of the abundant data from AstraZeneca's own extensive regulatory testing, it would only serve to further underscore rosuvastatin calcium's chemical stability shortcomings. The problem of variability — one batch showing materially different impurity levels than a second batch — is itself a significant issue with rosuvastatin calcium. Tr. 864:11-23. The need in pharmaceuticals for accuracy and precision is incompatible with batch-to-batch variability and inconsistencies. *Id*. Indeed, rosuvastatin calcium's variability issue was repeatedly highlighted by AstraZeneca chemists. DTX-721 at 4, 5, DTX-727 at 2; Tr. 864:11-23. Watson's rosuvastatin zinc, on the other hand, consistently shows negligible B2 levels, as detailed above, further confirming the substantial chemical stability differences between the two salts.

Plaintiffs do mention one of their own, more recent rosuvastatin calcium batches, which happens to show low B2 levels. Br. at 14. Conspicuously absent from their discussion, however, is the fact that this batch is only one of potentially hundreds manufactured in 2010. Tr. 461:15-462:11; D.I. [393] at 3. Plaintiffs' token sample size of one cannot overcome the mountain of evidence showing rosuvastatin calcium's substantial chemical stability limitations — restrictions that were overcome by Watson's rosuvastatin zinc.

Plaintiffs also attempt to deflect attention from the chemical stabilizer in its Crestor® formulation by pointing to a stabilizer-free formulation Egis tried to develop for rosuvastatin calcium. Br. at 15. Plaintiffs neglect to mention, however, that Egis's rosuvastatin calcium formulation failed regulatory testing and was abandoned. Tr. 508:22-509:10. Plaintiffs cannot escape the implications of its chemical stabilizer by hiding behind failed research and development efforts by Egis.

Plaintiffs' go on to make unfounded assertions regarding Cobalt Pharmaceuticals, Inc.'s rosuvastatin calcium ANDA (which Watson acquired in late 2010), suggesting that Cobalt's rosuvastatin calcium did not show any levels of B2. Br. at 14. The documentary evidence, however, belies this assertion. While Cobalt's proposed specification does not separately identify the B2 impurity, the specification does include a category called "unknown impurities," which is included to cover unspecified impurities at levels up to 0.5%. PTX-322 at 2. This catch-all category can reflect an accommodation for B2 levels as high as 0.5%, as Plaintiffs' expert acknowledged at trial. Tr. 463:21-464:22. It is also telling that Cobalt, like AstraZeneca, apparently had to add a "pH modifier" or stabilizer to its rosuvastatin calcium formulation. PTX-325 at 24, 28.

There is even a suggestion by Plaintiffs that the elevated B2 levels in rosuvastatin calcium were solved by changing one of their manufacturing steps. PPFF ¶ 142. Years after implementing the so-called "fix" in 1999 or 2000 (Tr. 186:16-23), however, many batches still showed B2 levels several times the normal threshold. For example, two out of eleven tested batches of bulk rosuvastatin calcium manufactured in 2003 showed B2 levels above the normal threshold within one year of storage, one reaching B2 levels of 0.65% by the second year. DTX-793 at 11-12, 20, 24; Tr. 924:3-15. And at least two tested tablet batches manufactured in 2005

showed B2 levels above the normal 0.5% threshold within one year of storage. DTX-795 at 86, 130. Not surprisingly, AstraZeneca continued searching for a replacement rosuvastatin salt, even after altering the manufacturing process. Indeed, the search continued for many years, citing as motivation the chemical stability limitations of rosuvastatin calcium. DTX-721 at 3-4, 11-13, 18-19, DTX-723 at 1, DTX-727 at 1, DTX-729 at 1, DTX-733 at 1, DTX-742 at 1, DTX-748 at 1, DTX-750 at 1. The record contradicts Plaintiffs' suggested manufacturing "fix."

Following on the heels of the suggested manufacturing fix, Plaintiffs try to make much of the fact that in 2010 they were allegedly able to lower the total impurity specification for rosuvastatin calcium to around the same level Watson has already established for its rosuvastatin zinc. Br. at 14. That it took AstraZeneca and its hordes over ten years of studying and working on rosuvastatin calcium to achieve total impurity levels readily seen in Watson's rosuvastatin zinc only speaks to the substantial differences between these two salts. More importantly, though, Plaintiffs' citation to the total impurity level rather than individual impurity levels masks the fact that the B2 impurity specification for its Crestor® product remains at multiple times the normal threshold, despite all of their work on the salt. PTX-1326 at 29.

Fundamentally, Plaintiffs mischaracterize the influence the manufacturing process has on chemical stability. *See* Br. at 13-14. There is no dispute that the way a salt is made can affect its impurity profile. After all, if one adds in or fails to remove unwanted ingredients, the chance of ending up with an impure salt increases. Tr. 1032:19-24. But the method of making the salt is not the *only* factor that can affect the impurity profile. *See, e.g.*, PTX-62-T at 2, PTX-469-T-D at 1 (". . . the impurity profile *also* depends on the synthesis route . . . ." (*emphasis* added)); Tr. 837:16-21. The cation used to form the salt plays a central role in chemical stability, as AstraZeneca's own alternative rosuvastatin salt investigation confirms. To address the B2 issue

in rosuvastatin calcium, AstraZeneca did not simply investigate the way they were making it — they *investigated other salts of rosuvastatin*. If the identity of the counterion had no material influence on chemical stability, AstraZeneca's chemists simply wasted substantial amounts of time and money investigating other rosuvastatin salts. *See supra* (III)(A)(4). The undisputed evidence confirms that Watson's rosuvastatin zinc is substantially different from rosuvastatin calcium in terms of chemical stability, a critical physical-chemical property for pharmaceutical salts.

2. Substantial Differences In Hygroscopicity

Watson's rosuvastatin zinc is also substantially different in its tendency to resist water-uptake. Rosuvastatin calcium is undisputedly hygroscopic — regulatory qualification tests conducted by AstraZeneca indicate that the water content of a late development batch stored at the relatively mild conditions of 20°C±4°C and 50%RH increased 3.39% after only one day. DFF ¶ 79. Watson's rosuvastatin zinc, meanwhile, shows a water content increase of just 0.4% at the even harsher conditions of 25°C±1°C and 80%±2% RH. *Id*. While Egis's DMF conservatively characterizes the rosuvastatin zinc material as "slightly hygroscopic", even chemists at AstraZeneca itself have more appropriately characterized such material as "nonhygroscopic." *Id.*

AstraZeneca had to establish a broad water content specification to accommodate rosuvastatin calcium's predisposition for gaining water. The specification window permits levels ranging from completely dry (i.e., 0% water content) to up to 6% water content. DFF ¶ 80. The need for this wide window is confirmed by data collected from stability tests. Indeed, a representative batch showed water content jumping from 2.7% to 4.1% after just six months. *Id*. The water content specification for Watson's rosuvastatin zinc, on the other hand, reflects the

salt's resistance to water-uptake. Watson was able to establish a narrow 2% window for its salt, only permitting water content levels between 6% and 8%. *Id*. Conforming to expectation, long-term stability data from samples of Watson's rosuvastatin zinc show negligible water content change over time. *Id*.

Plaintiffs seem to suggest that these hygroscopicity differences are insignificant because the salts' water content specifications each permit a salt with 6% water content. Br. at 16. This argument misses the mark. The issue for pharmaceuticals is not its initial water content, or the water content at a specific time, for that matter. Rather, the issue is whether and how that water content *changes* over time. *See supra* (III)(A)(3)-(4). Water content changes can significantly affect the accuracy and precision of pharmaceutical manufacturing, and can interfere with a drug's stability.[13]

Plaintiffs also label rosuvastatin calcium's substantially greater hygroscopicity "unimportant" because the recommended handling and storage conditions for rosuvastatin calcium and rosuvastatin zinc are similar. Br. at 15-16. The recommended storage conditions, however, are designed not only in view of rosuvastatin's sensitivity to moisture, but also its sensitivity to other elements, such as heat and light. DTX-858 at 480, 484, 502; PTX-18 at 5. Although rosuvastatin zinc's substantially improved hygroscopicity may not have been enough on its own to overcome rosuvastatin's other sensitivities, it does not alter the fact that the hygroscopicity differences are substantial.

[13] Plaintiffs also point to water content specifications for the finished drug tablets. Br. at 16. Water content changes in finished tablets, however, have little, if any, relation to the active ingredient and thus have no reasonable bearing on the equivalence analysis here. Because the amount of active ingredient in the tablets is so small compared to the amount of the other ingredients, any tendency of the active ingredient to uptake water, or lack thereof, is overshadowed by the hygroscopicity of the other ingredients. *See, e.g.*, DTX-858 at 517, DTX-859 at 2.

In sum, while Plaintiffs now in litigation try to downplay the significance of Watson's rosuvastatin zinc showing near non-hygroscopicity, the record, including internal documents prepared by AstraZeneca chemists, confirm that this improved hygroscopicity is a substantial difference and advantage over rosuvastatin calcium.

3. Substantial Differences In Crystal Formation and Physical Stability

Another substantial difference between the two salts is rosuvastatin zinc's ability to form a stable crystalline solid and remain physically stable over time. Extensive testing showed that Watson's rosuvastatin zinc retained its crystallinity even after six months at conditions harsher than the recommended storage conditions. DFF ¶ 81. Even after formulated and pressed into tablets, moreover, Watson's rosuvastatin zinc showed no material change in its crystalline form. *Id*.

Rosuvastatin calcium, on the other hand, has proved difficult to crystallize. Shionogi chemists, despite their best efforts, were never able to prepare rosuvastatin calcium in crystalline form. DFF ¶ 82. And while AstraZeneca chemist Nigel Taylor was eventually able to crystallize rosuvastatin calcium, the crystalline form proved highly hygroscopic (even more than the amorphous calcium rosuvastatin salt) and unstable. *Id*. Indeed, despite identifying a rosuvastatin calcium crystal form early in the development process, AstraZeneca chose not to develop it as a replacement, companion, or follow-on to the amorphous form. *Id*.

Plaintiffs erroneously assert that Watson's rosuvastatin zinc loses crystallinity if dried at temperatures above 30ºC. Br. at 12. While Egis did conservatively suggest a *recommended* drying temperature of 30ºC, Plaintiffs' own underlying document shows that a sample of Watson's rosuvastatin zinc remained crystalline even after being dried at the higher temperature of 40ºC. PTX-20 at 26. Regardless, there is no evidence that the recommended 30ºC drying

temperature is onerous or even uncommon in the industry. Thus, Egis's conservative recommendation does not overcome the undisputed evidence of substantial physical stability differences.

Plaintiffs further challenge the physical stability of Watson's rosuvastatin zinc by pointing to data showing that one sample of the salt lost crystallinity after being heated to 50ºC and suffering water loss. Br. at 12-13; PTX-20 at 26. This is hardly surprising — AstraZeneca and Plaintiffs' expert Dr. Bugay described 50ºC as an "extreme" and "very high" temperature for pharmaceutical salts. DTX-858 at 484; Tr. 395:5-20. And Plaintiffs' fail to mention, moreover, that *all* crystalline hydrates (such as Watson's rosuvastatin zinc) lose crystallinity after heating to the point of water loss. Tr. 1009:15-1010:13. Regardless, even if Watson's rosuvastatin zinc behaves like all other crystalline hydrates in showing some reaction to water loss, given the choice between a pharmaceutical salt that is sensitive to water loss and one that has a strong tendency to gain water, those in the industry would always choose water-loss-sensitive salts like Watson's rosuvastatin zinc. Tr. 1043:1-5.[14]

4. Plaintiffs' Alleged Evidence Of Insubstantial Differences Between Watson's Rosuvastatin Zinc Salt And The Claimed Rosuvastatin Calcium Salt Fails As A Matter Of Law

Plaintiffs' alleged evidence of insubstantial differences between the two rosuvastatin salts fails as a matter of law. Plaintiffs spend several pages of their Brief discussing the alleged pharmacokinetic performance of Watson's rosuvastatin zinc and its resulting bioequivalence to Plaintiffs' Crestor® product. Br. at 6-11. The Federal Circuit recently confirmed, however, that

[14] Despite overtures at trial, Plaintiffs make no mention in their brief of the allegation that Watson's rosuvastatin zinc salt is a mixture containing about 50% amorphous material, . Plaintiffs' reluctance is likely due to the numerous flaws in Dr. Bugay's underlying testing (DFF ¶ 84) and Dr. Morris's more reliable conclusion that Watson's rosuvastatin zinc contains negligible (slightly more than 2%) amorphous material. DFF ¶ 83.

bioequivalence under FDA regulations is distinct from equivalence under the doctrine of equivalents, and is insufficient to establish infringement. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009). Indeed, the Federal Circuit was even more direct in an earlier opinion: "FDA equivalence is irrelevant to patent law because it involves fundamentally different inquiries." *The Johns Hopkins Univ. v. Datascope Corp.*, 543 F.3d 1342, 1349 n.3 (Fed. Cir. 2008). Here, Plaintiffs' evidence of pharmacokinetic performance and bioequivalence is the same type of evidence dismissed by the Federal Circuit as insufficient to establish infringement, as a matter of law.

Attempting to evade this Federal Circuit precedent, Plaintiffs feign evidence beyond mere bioequivalence by separately discussing "tablet dissolution" and "solubility." Br. at 7-10. These "properties," however, go hand-in-hand with and are subsumed within bioequivalence. The bioavailability of a drug taken in the form of a tablet, like Watson's rosuvastatin zinc, is a direct result of and is dependent on both the tablet dissolving as well as the drug subsequently dissolving and entering the body's fluids. DTX-684 at 5-6; PTX-17 at 2, PTX-1254 at 2, PTX-1292-A at 21, 27-28, PTX-1323-A at 21, 27-28; Tr. 228:10-229:19, 259:6-260:9. Plaintiffs' separate discussion of "tablet dissolution" and "solubility" thus offers no additional support for Plaintiffs' legally deficient bioequivalence argument. Plaintiffs cannot enlarge their insufficient proof by cutting it up into pieces.

C. Watson's Rosuvastatin Zinc Salt Is Substantially Different From The Other Claimed Rosuvastatin Salts

Though less data is available, undisputed evidence shows substantial physical-chemical differences between Watson's rosuvastatin zinc salt and the other claimed rosuvastatin salts. Sodium rosuvastatin, for example, gains so much water at mild humidity levels that it actually liquefies. DFF ¶ 85. Indeed, rosuvastatin sodium's extreme hygroscopicity was the motivation

for Shionogi to switch its development focus to the calcium salt. *Id.* The record also shows that to the extent it is even possible to crystallize rosuvastatin sodium, the resulting crystals are hygroscopic and physically unstable. *Id.* Again, Watson's rosuvastatin zinc, in contrast, has negligible hygroscopicity and readily forms a physically stable crystalline solid. *See supra* (III)(B)(2)-(3).

Data collected from the ammonium and magnesium salts of rosuvastatin likewise show elevated hygroscopicity, as well as chemical instability. DFF ¶ 86. Rosuvastatin magnesium, moreover, has a melting point that is impractically low for manufacturing pharmaceuticals. *Id.* And while AstraZeneca was able to prepare ammonium rosuvastatin and magnesium rosuvastatin in crystalline form, the resulting structures are much more complex and thus more difficult to handle compared to Watson's rosuvastatin zinc. *Id.*

The potassium salt, meanwhile, proved physically unstable and reluctant to crystallize. DFF ¶ 87. And the lithium salt of rosuvastatin presented a significant potential for toxicity in humans, and was quickly abandoned by AstraZeneca. *Id.* This potential toxicity stands in stark contrast to Watson's rosuvastatin zinc, which has received tentative approval for marketing in the United States by the FDA and has caused no serious adverse events in human testing. *Id.*

Plaintiffs make no serious attempt to carry their burden of proving equivalence between Watson's rosuvastatin zinc salt and the remaining claimed rosuvastatin salts. Plaintiffs' failure of proof is particularly troubling in light of their continued assertion that Watson's rosuvastatin zinc infringes claim 7, which covers only the sodium salt of rosuvastatin. Plaintiffs' argument for equivalence between Watson's rosuvastatin zinc and the other claimed salts rests on a single after-thought question posed to their expert Dr. Bugay at the very end his direct examination. Tr. 435:19-436:7. Plaintiffs' vague question and Dr. Bugay's conclusory response cannot

sustain a finding of equivalence. Plaintiffs' evidence fails even under their improper anything-that-delivers-rosuvastatin test. *See* Br. at 6. There is no indication that any rosuvastatin salts other than the calcium salt was tested in humans. Thus, there can be no sufficient evidence showing that these other rosuvastatin salts can deliver rosuvastatin in the body, let alone that they deliver rosuvastatin in substantially the same way as Watson's rosuvastatin zinc.

IV. CONCLUSION

For the foregoing reasons, as well as those contained in Watson's Proposed Findings of Fact and the Joint Statement of Undisputed Facts, Watson respectfully requests that the Court declare that Watson does not infringe Claims 6, 7 and 8 of the '314 patent, and that Watson is legally entitled to obtain final FDA approval for its rosuvastatin zinc NDA.

Respectfully submitted,

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, David E. Moore, hereby certify that on February 28, 2013, the attached document was electronically filed with the Clerk of the Court using CM/ECF which will send notification to the registered attorney(s) of record that the document has been filed and is available for viewing and downloading.

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